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Concl'd

Y is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q<sub>1</sub>)(Q<sub>2</sub>), O(Q<sub>1</sub>), halo, S(Q<sub>1</sub>), or CN;

each q<sub>1</sub> is, independently, from 2 to 10;

each q<sub>2</sub> is, independently, 0 or 1;

m is 0, 1 or 2;

p is from 1 to 10; and

q<sub>3</sub> is from 1 to 10 with the proviso that when p is 0, q<sub>3</sub> is greater than 1.

#### REMARKS

The specification has been amended to reflect the claim of priority. After entry of the above amendment, claims 1-13, 18, and 21-32 will be pending. These claims find support throughout the specification and claims as originally filed.

Applicants have amended the specification to specifically identify sequences with SEQ ID NOS. Applicants have further amended the specification to update SEQ ID NOS and to correct minor typographical errors. No new matter has been added.

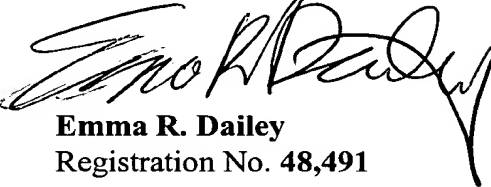
Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

**DOCKET NO: ISIS-4789**

**PATENT**

Applicants respectfully request that this amendment be entered and that claims 1-13, 18, and 21-32 be allowed at this time.

Respectfully submitted,



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DOCKET # F 2533660

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

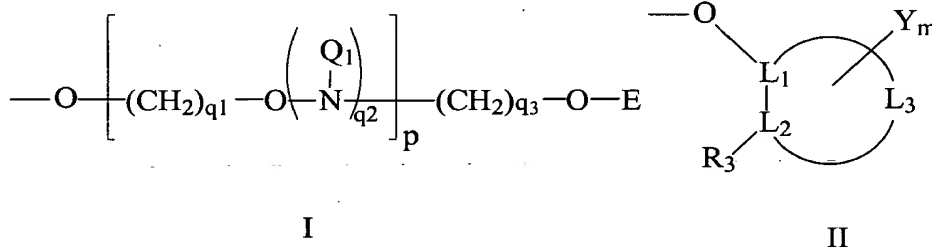
## In the Claims

Please cancel claims 14-17, 19-20 and 33-36, without prejudice, and amend claims 1 and 4 as presented below:

1. (Amended) An oligonucleotide comprising a plurality of nucleotides, wherein:  
a first portion of said plurality of nucleotides have B-form conformational geometry and are joined together in a continuous sequence, at least two of said nucleotides of said first portion being ribonucleotides [or arabinonucleotides]; and

a further portion of said plurality of nucleotides are ribonucleotide that have A-form conformation geometry and are joined together in at least one continuous sequence.

4 (Amended). The oligonucleotide of claim 1 wherein each nucleotide of said further portion, independently, is a 2'-fluoro nucleotide or a nucleotide having a 2'-substituent having the formula I or II:



wherein

E is C<sub>1</sub>-C<sub>10</sub> alkyl, N(Q<sub>1</sub>)(Q<sub>2</sub>) or N=C(Q<sub>1</sub>)(Q<sub>2</sub>);

each Q<sub>1</sub> and Q<sub>2</sub> is, independently, H, C<sub>1</sub>-C<sub>10</sub> alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support, or Q<sub>1</sub> and

Q<sub>2</sub>, together, are joined in a nitrogen protecting group or a ring structure optionally containing [that can include] at least one additional heteroatom selected from N and O;

R<sub>3</sub> is OX, SX, or N(X)<sub>2</sub>;

each X is, independently, H, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C(=NH)N(H)Z, C(=O)N(H)Z or OC(=O)N(H)Z;

Z is H or C<sub>1</sub>-C<sub>8</sub> alkyl;

L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub> form a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Y is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q<sub>1</sub>)(Q<sub>2</sub>), O(Q<sub>1</sub>), halo, S(Q<sub>1</sub>), or CN;

each q<sub>1</sub> is, independently, from 2 to 10;

each q<sub>2</sub> is, independently, 0 or 1;

m is 0, 1 or 2;

p is from 1 to 10; and

q<sub>3</sub> is from 1 to 10 with the proviso that when p is 0, q<sub>3</sub> is greater than 1.